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Does pharmacological conditioning with the volatile anaesthetic  
sevoflurane offer protection in liver surgery?

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## ORIGINAL ARTICLE

# Does pharmacological conditioning with the volatile anaesthetic sevoflurane offer protection in liver surgery?

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## Abstract

**Background:** A recently published randomized control trial (RCT) showed a protection of the remnant liver from ischemia-reperfusion (I/R) injury by pharmacological pre-conditioning with a volatile anaesthetic in patients undergoing hepatic resection. Whether the continuous application of volatile anaesthetics (pharmacological conditioning) also protects against I/R injury is unknown.

**Methods:** Consecutive patients undergoing liver resection with inflow occlusion from 2005–2007 were included in the trial. Two groups of anaesthesia regimens with either continuous application of the volatile anaesthetic sevoflurane (pharmacological conditioning) or continuous infusion of the intravenous (i.v.) anaesthetic propofol (control group) were compared. Endpoints were serum-peak-aspartate aminotransferase (AST)/ alanine aminotransferase (ALT) levels, length of stay (LOS) and intensive care unit (ICU) stays, and the occurrence of post-operative complications.

**Results:** Two hundred and twenty-seven patients were included. Pharmacological conditioning did not protect the remnant liver from IR injury (adjusted difference for peak-AST:61.9 U/l, 95% confidence interval (CI): -151.7–275.4 U/l,  $P = 0.568$ ; peak-ALT:136.1 U/l, 95% CI: -113.7–385.9 U/l,  $P = 0.284$ ) nor reduce LOS (adjusted difference 0.9 days, 95% CI: -2.6–4.3 days,  $P = 0.622$ ) or ICU stay (1.6 days, 95% CI: -0.2–3.3 days,  $P = 0.079$ ), and was not associated with reduced complication rates (adjusted OR 1.12, 95% CI:0.6–2.3,  $P = 0.761$ ) compared with the control group.

**Conclusion:** In this retrospective study, continuous volatile anaesthesia in liver resection does not provide protection of the remnant liver from IR injury compared with continuous i.v. anaesthesia.

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## Introduction

A recently published randomized controlled trial (RCT) showed that volatile anaesthesia confers protection against ischemia-reperfusion (I/R) injury in patients undergoing hepatic resection with inflow occlusion.<sup>1</sup> I/R injury in the liver is caused by

clamping of the portal triad (inflow occlusion) that is used to prevent intra-operative blood loss during hepatic resections.<sup>2–5</sup> Both intra-operative blood loss and I/R injury are associated with an increased risk of post-operative complications and mortality.<sup>6–9</sup> The challenge is, therefore, to find a balance between reducing intra-operative blood loss by using an inflow occlusion procedure, and to minimize an I/R injury caused by the inflow occlusion.

Intermittent clamping of the portal triad as well as ischaemic preconditioning has been shown to reduce I/R injury of the remnant liver.<sup>10–15</sup> We recently observed protection against

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ischaemic injury through pharmacological preconditioning with sevoflurane, a commonly used volatile anaesthetic agent.<sup>1</sup> While ischaemic preconditioning is time-consuming and intermittent clamping might lead to increased intra-operative blood loss, pharmacological preconditioning is an easily applicable non-invasive method. However, the timing between preconditioning and inflow occlusion might be difficult. In addition, utilization of preconditioning is not possible in emergency situations where hepatic inflow occlusion cannot be preceded by pharmacological preconditioning. An alternative could be the use of continuous volatile anaesthetics throughout surgery (pharmacological conditioning). The aim of this study was, therefore, to compare pharmacological conditioning with sevoflurane with intravenous (i.v.) anaesthesia performed with propofol with post-operative liver function as the primary endpoint. We hypothesized that the continuous application of volatile anaesthetics with sevoflurane (pharmacological conditioning) would protect the remnant liver from I/R injury.

## Materials and methods

### Study design

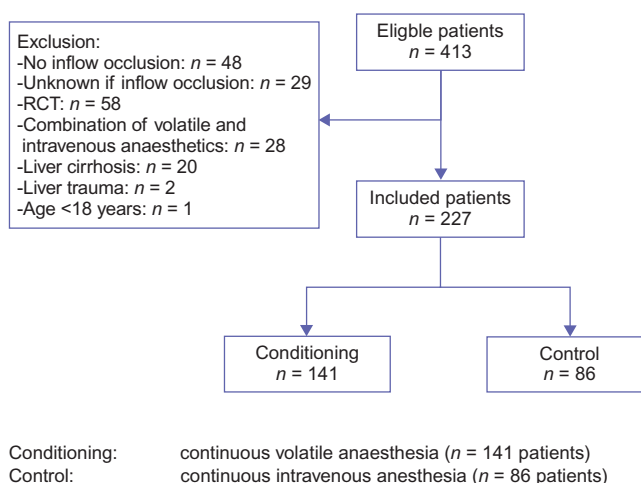
Data were collected from a database with prospectively collected data from all patients treated at the Swiss Hepato-Pancreato-Biliary (HPB) Center at the University Hospital of Zurich, Switzerland.<sup>1,16,17</sup> For this analysis, we included consecutive patients undergoing any type of liver resection with inflow occlusion for benign or malignant diseases between 1 January 2005 and 31 December 2007 with an anaesthesia with either the i.v. applied anaesthetic propofol or the volatile anaesthetic sevoflurane for the entire surgical procedure. Control patients with propofol anaesthesia from a recently completed RCT<sup>1</sup> were included as well. Patients receiving pharmacological preconditioning with volatile anaesthetics as well as patients with liver trauma or liver cirrhosis were excluded. Also patients operated without inflow occlusion during surgery were not considered for this study. Patients were also excluded with a combination of volatile and i.v. anaesthetics during liver surgery as a result of a high variability of dose and ratio of these anaesthetics and resultant heterogeneity within this group of patients (Fig. 1).

The study was approved by the institutional review board for human studies and internationally registered at <http://clinicaltrials.gov> (NCT01021228).

### Anaesthesia

We compared two groups of patients who received either the volatile anaesthetic sevoflurane (pharmacological conditioning) or the i.v. anaesthetic propofol (control) (Fig. 2).

All patients received oral midazolam (7.5 mg) pre-operatively for premedication. If desired and necessary, a thoracic epidural anaesthesia was performed for post-operative pain control using continuous application of ropivacaine (0.33% during surgery and 0.2% in the post-operative phase). Both groups received the same



**Figure 1** Flow chart of the study design. RTC, randomized control trial

induction of anaesthesia according to the standardized procedures with fentanyl and atracurium as boluses according to clinical need and remifentanyl.

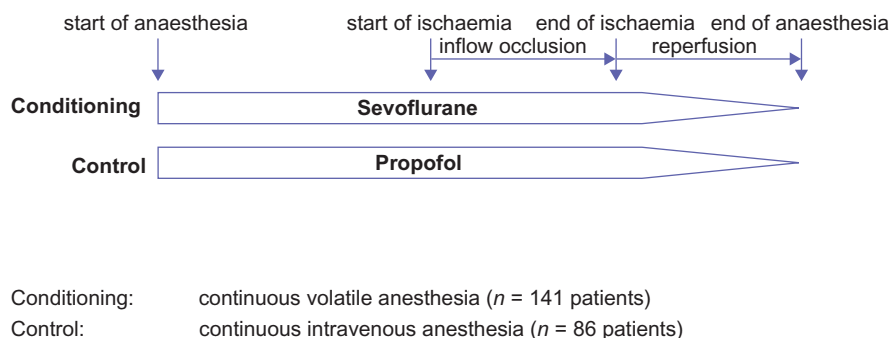
Allocation to one of the two anaesthesiological approaches was entirely up to the discretion of the attending anaesthesiologist. Anaesthesiologists were more likely to use conditioning anaesthesia in patients with severe co-morbidities owing to its better cardio-vascular tolerance compared with an i.v. anaesthetic. This may have introduced confounding by indication that we tried to minimize as described in the statistical analysis section below. The pharmacological 'conditioning group' received a continuous volatile anaesthesia with sevoflurane of 1.0–2.5 vol % (according to age-related minimum alveolar concentration) during the liver surgery. The 'control group' was anaesthetized with propofol (plasma target concentration of 2–4 µg/ml) during the liver surgery. Some of these patients had participated as control patients in a previous RCT<sup>1</sup> (Fig. 2).

### Surgical procedure

The hepatic surgery was performed exclusively by surgeons specialized in HPB surgery according to international surgical standards for transection of liver parenchyma. For the liver resection, a low central venous pressure (CVP) from 0 to 5 mmHg was required to prevent a high intra-operative blood loss.<sup>14,18,19</sup> The parenchymal transections were done with the Kelly clamp crushing technique<sup>3</sup> under an inflow occlusion procedure.<sup>2–4,12</sup> The tourniquet technique around the portal triad was used as inflow occlusion.<sup>14</sup> The peri-operative management was performed according to the surgical standards of the operating procedure and to the standard care of the HPB centre.

### Endpoints

The primary endpoint was the serum peak level of aspartate-aminotransferase (AST) representing the IR injury of the liver



**Figure 2** Study design

after a hepatic resection. Secondary endpoints were the serum peak level of alanine aminotransferase (ALT), intra-operative blood loss and lengths of hospital stay (LOS) as well as intensive care unit (ICU) stay. According to the Clavien-Dindo classification,<sup>20</sup> mortality and morbidity were assessed as additional secondary endpoints. Post-operative complications were reported and analysed for the presence of any complication from grade I to grade V according to the Clavien-Dindo classification.<sup>20</sup> We specifically assessed the occurrence of high relevant complications such as grade III (requiring an intervention), IV (requiring ICU stay) or V (death).

### Statistical analysis

We did not have any missing variables for the primary and secondary endpoints. Regarding potential confounders, only 1.8% of baseline ALT levels (all from the conditioning group) and 4.4% of baseline bilirubin levels (nine missing values in the conditioning and one missing in the control group) were missing, whereas the collection of all other factors was complete. Because of the small amount of missing data, we decided to replace these missing values by the median of the available data and did not use more advanced techniques for missing data such as multiple imputation.

In a first step of the analysis, we expressed the distribution of variables using means and standard deviation (SD) for normally distributed data, and medians and interquartile ranges for non-normally distributed data. We tested data for normality with the Kolmogorow–Smirnow test<sup>21</sup> and performed quantile–quantile plots of dependent variables.<sup>22</sup>

We compared the primary endpoint (serum peak level of AST) between the two groups using simple linear regression (without adjustment for confounders) and in the main analysis, a multivariable linear regression model with peak serum AST level as the dependent, and group allocation as the independent variable. Potential confounders for which we adjusted in the multivariable linear regression analyses were age, pre-operative chemotherapy (yes/no), steatosis (yes =  $\geq 5\%$ /no =  $< 5\%$ ), the American Society of Anesthesiologists (ASA) physical status classification, inflow occlusion time, and baseline AST/ALT and

bilirubin levels. We confirmed that the assumptions for linear regression, i.e. the linearity of the relationship between dependent and independent variables, homoscedasticity (constant variance) of the errors and normality of the error distribution, were met.<sup>23</sup> We repeated these analyses for the secondary endpoints. For the binary outcomes ‘any complication’ or ‘complications higher than IIIB’ (severe complication), we also applied simple and multivariable models, but used logistic regression analysis. For all results, we reported point estimates, 95% confidence intervals (CI) and *P*-values ( $\leq 0.05$  considered significant). We performed the statistical analyses using the statistical program STATA (version 11; Stata Corp., College Station, TX, USA).

## Results

### Study population

Two hundred and twenty-seven patients undergoing liver resections with inflow occlusion were included in the study (Fig. 1). One hundred and forty-one patients received a continuous volatile anaesthesia with sevoflurane (‘conditioning group’), whereas 86 patients received continuous i.v. anaesthesia with propofol (‘control group’).

Patients’ characteristics are presented in Table 1. Patients of the control group were younger [56.3 years (standard deviation (SD) 12.7 years)] compared with the conditioning group [59.2 years (14.8 years)]. ASA score was higher in the conditioning group (ASA score III or IV: 38.3%) compared with the control group (16.3%). A steatosis degree of higher than 30% was more often observed in patients of the control than in the conditioning group (43% versus 33%). The presence of malignant disease was similarly distributed in both groups (75.2–81.4%). Baseline AST levels were higher in the conditioning group [mean 50.1 U/l [47.8 U/l]] than in the control group (mean 45.7 U/l [49.4 U/l]). Operation time, duration of inflow occlusion and CVP during surgery were similar among both groups (Table 2). Fifty per cent of the patients in the conditioning group underwent a major liver resection ( $\geq 3$  Couinaud’s liver segments) and 42% patients in the control group.

**Table 1** Patients' characteristics

	Conditioning (n = 141)	Control (n = 86)
Age (years), mean (SD)	59.2 (14.8)	56.3 (12.7)
Gender male/female (%)	88/53 (62.4%/37.6%)	49/37 (57%/43%)
ASA		
median (IQR)	2 (2–3)	2 (2)
I&II (%)	87 (61.7%)	72 (83.7%)
III&IV (%)	54 (38.3%)	14 (16.3%)
Charlson, mean (SD)	5.1 (3.4)	6.0 (3.6)
Steatosis		
≤30%	95 (67.4%)	49 (57.0%)
>30%	46 (32.6%)	37 (43%)
Fibrosis no/yes (%)	105/36 (74.5%/25.5%)	68/18 (79.1%/20.9%)
Pre-operative chemotherapy (%)	38 (27%)	39 (45.4%)
Malignant/benign disease (%)	106/35 (75.2%/24.8%)	70/16 (81.4%/18.6%)
Primary disease (%)		
Echinococcosis	7 (5.0%)	3 (3.5%)
Colorectal metastasis	37 (26.2%)	36 (41.9%)
Neuroendocrine tumour	3 (2.1%)	2 (2.3%)
Hepatocellular carcinoma	27 (19.1%)	11 (12.8%)
Cholangiocarcinoma	19 (13.5%)	10 (11.6%)
Other benign lesions	26 (18.4%)	13 (15.1%)
Other malignant lesions	22 (15.6%)	11 (12.8%)
Baseline ALT (U/l), mean (SD)	63.4 (93.7)	51.9 (67.1)
Baseline AST(U/l), mean (SD)	50.1 (47.8)	45.7 (49.4)
Baseline bilirubin (μmol/l), mean (SD)	18.8 (37.8)	16.3 (30.8)

Conditioning, continuous volatile anaesthesia, control, continuous intravenous anaesthesia; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ASA, American Society of Anesthesiologists; IQR, interquartile range; SD, standard deviation.

### Is there a protection against I/R injury of the liver after hepatic resection by continuous application of volatile anesthetics?

Compared with the *control* group with propofol anesthesia, a continuous application of volatile anesthetics (*conditioning*) did not reduce serum peak levels of AST (adjusted difference for AST 61.85 U/l, 95%CI −151.66–275.38 U/l,  $P = 0.568$ ). Serum peak levels of ALT (adjusted difference 136.06 U/l, 95%CI −113.77–385.90,  $P = 0.284$ ) were also not significantly different (Table 3).

### Does conditioning with the volatile anesthetic sevoflurane improve the post-operative outcome?

Seventy-eight patients of the conditioning group (55.3%) and 42 patients of the control (48.8%) developed a post-operative complication. Table 2 shows the frequency of post-operative complications. 30-days-mortality was higher in the conditioning group (4.3%) than in the control group (2.3%).

No statistically significant differences in serum peak levels of bilirubin or creatinine, blood loss, or length of hospital or ICU stay were detected comparing the conditioning with the control

group (Table 3). Seventy-eight patients of the conditioning group (55.3%) developed a post-operative complication compared with the control group (48.8%) [adjusted odds ratio (OR) 1.12, 95%-CI 0.6–2.3,  $P = 0.761$ ]. Patients of the conditioning group did not suffer significantly more often from a grade IIIb to V complication than the control group (20.6% versus 12.8%; adjusted OR 0.84, 95%-CI 0.4–2.0,  $P = 0.688$ ) (Table 3). The mortality rate was similar in both groups (2.3% versus 4.3%, adjusted OR 0.63, 95% CI 0.1–5.1,  $P = 0.668$ ) (Table 3).

### Discussion

The continuous application of the volatile anaesthetic sevoflurane did not show a protection from I/R injury in liver surgery and provided similar clinical outcomes as compared with the continuous application of i.v. anaesthetic propofol.

Volatile anaesthetic agents attenuate cardiac mechanical dysfunction after ischaemia in the myocyte,<sup>24,25</sup> and preserve hepatic blood flow and cell function after ischaemia of the liver.<sup>26,27</sup> Although i.v. anaesthetics such as propofol do not seem to have

**Table 2** Intra- and post-operative parameters

Intra-operative	Conditioning (n = 141)	Control (n = 86)
Operation time (minutes), mean (SD)	289.1 (133.4)	279.6 (121.6)
Inflow occlusion (minutes), mean (SD)	35.5 (13.6)	33.4 (8.5)
Minor/major resection (%)	70/71 (49.7%/50.3%)	50/36 (58.1%/41.9%)
Central venous pressure (mmHg), mean (SD)	3.6 (2.9)	3.4 (2.5)
Post-operative outcome		
Morbidity (%)	78 (55.3%)	42 (48.8%)
Mortality (%)	8 (5.7%)	2 (2.3%)
Post-operative complications		
None complications	63 (44.7%)	44 (51.2%)
Grade I	10 (7.1%)	6 (7%)
Grade II	23 (16.3%)	17 (19.8%)
Grade IIIa	16 (11.3%)	8 (9.3%)
Grade IIIb	8 (5.7%)	3 (3.5%)
Grade IVa	10 (7.1%)	4 (4.6%)
Grade IVb	5 (3.5%)	2 (2.3%)
Grade V (30-days-mortality)	6 (4.3%)	2 (2.3%)

Conditioning, continuous volatile anaesthesia; control, continuous intravenous anaesthesia; SD, standard deviation.

**Table 3** Primary and secondary outcome results

Outcome	Conditioning (n = 141)	Control (n = 86)	Unadjusted difference (95% CI, P-value)	Adjusted difference (95% CI, P-value)
Peak AST, mean (SD) U/l	629.0 (782.6)	592.5 (695.9)	36.52 (-158.26–231.30, P = 0.712)	61.85 (-151.66–275.38, P = 0.568)
Peak ALT, mean (SD) U/l	615.2 (845.5)	554.1 (582.9)	61.11 (-124.87–247.09, P = 0.518)	136.06 (-113.77–385.90, P = 0.284)
Peak bilirubin, mean (SD) $\mu$ mol/l	56.2 (84.3)	46.15 (64.1)	10.00 (-7.59–27.60, P = 0.263)	9.40 (-15.79–34.58, P = 0.462)
Peak creatinine, mean (SD) $\mu$ mol/l	108.8 (56.8)	95.7 (47.7)	13.14 (-0.53–26.81, P = 0.060)	-0.28 (-16.93–16.36, P = 0.973)
Blood loss, mean (SD) ml	491.5 (572.6)	396.4 (364.3)	455.46 (389.17–521.76, P = 0.001)	43.21 (-101.46–187.88, P = 0.557)
Length of hospital stay in days, median (IQR)	12 (9–19)	11 (9–14)	2.97 (0.23–15.80, P = 0.034)	0.85 (-2.56–4.26, P = 0.622)
Length of ICU stay in days, median (IQR)	1 (0–3)	0	2.16 (0.66–3.66, P = 0.005)	1.55 (-0.18–3.28, P = 0.079)
			Unadjusted odds ratio (95% CI, p value)	Adjusted odds ratio (95% CI, p-value)
Any complication (grade I–V) (%)	78 (55.3)	42 (48.8)	1.30 (0.77–2.18, P = 0.325)	1.12 (0.55–2.28, P = 0.761)
More severe complication (grade IIIb–V) (%)	29 (20.6)	11 (12.8)	1.77 (0.85–3.7, P = 0.130)	0.84 (0.36–1.97, P = 0.688)
Mortality (%)	6 (4.3)	2 (2.3)	0.40 (0.08–1.91, P = 0.249)	0.63 (0.08–5.11, P = 0.668)

Conditioning, continuous volatile anaesthesia; control, continuous intravenous anaesthesia; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ICU, intensive care unit; IQR, interquartile range; SD, standard deviation; 95% CI, 95% confidence interval.

Adjusted for age, pre-operative chemotherapy (yes/no), steatosis (yes/no), ASA score, inflow occlusion time and baseline ALT/AST and bilirubin level.

comparable protective properties, they have been widely accepted as they have the advantages of fast onset, a short recovery time after the intervention as well as potentially less post-operative nausea and vomiting.<sup>28</sup>

The literature describes the protective effects of volatile anaesthetics upon pre-conditioning and post-conditioning application.<sup>29–33</sup> An anaesthetic preconditioning with volatile anaesthetics such as sevoflurane was studied extensively in cardiac surgery and could reveal a relevant protection of the I/R syndrome in *in vivo* models<sup>34,35</sup> as well as in RCTs.<sup>29</sup> Additionally, volatile anaesthetic post-conditioning protects the heart from I/R injury in cardiac surgery in animal and *in vitro* models<sup>33,36,37</sup> as well as in a clinical trial.<sup>31</sup> Furthermore, studies showed that the cardio-protective effect during cardiac surgery could be related to the dosage and/or duration of the application of volatile anaesthetics in the pre- or post-conditioning setting.<sup>38,39</sup>

For hepatic surgery, we demonstrated a beneficial effect of volatile anaesthetics performing a pharmacological preconditioning in our recently published RCT:<sup>1</sup> application of sevoflurane for 10 min before the Pringle manoeuvre resulted in lower peak values of transaminases and, for the first time described in the literature, also improved post-operative outcome with fewer complications after liver resection. Additionally, we showed in a subgroup analysis that patients with severe liver steatosis ( $\geq 30\%$ ) had a stronger protective effect of the volatile anaesthetic preconditioning on the I/R injury.<sup>1</sup>

After administration of continuous sevoflurane anaesthesia (conditioning), patients undergoing coronary artery surgery experienced a reduced myocardial damage as measured by cardiac troponin I release, a reduced incidence of post-operative myocardial infarction, less time on mechanical ventilation, a shorter length of stay on the ICU as well as in the hospital.<sup>31,40,41</sup> Therefore the use of volatile anaesthetics as conditioning in cardiac surgery is widely used and accepted,<sup>32,42</sup> but in non-coronary surgical settings it is contradictory as discussed.<sup>43</sup> Nevertheless, based mainly on data from studies performed in patients undergoing on-pump coronary artery bypass surgery, the American College of Cardiology and the American Heart Association Guidelines recommended in 2007 the use of a continuous application of volatile anaesthetics for non-cardiac surgery in patients at increased risk of post-operative myocardial infarction.<sup>44</sup> Interestingly, a recently published RCT revealed that patients undergoing non-cardiac surgery do not benefit from anaesthesia with volatile anaesthetics compared with an i.v. anaesthesia.<sup>45</sup> In accordance with those results from Zangrillo *et al.*, our data in liver surgery also did not demonstrate a protective effect of continuous application of volatile anaesthetics.<sup>45</sup> In the literature, two studies compared the effects of a continuous application of either volatile or i.v. anaesthetics in liver surgery.<sup>46,47</sup> Similar to our present results, Song *et al.* also failed to present in a RCT any significant differences in peak serum ALT/AST comparing patients with a continuous application of volatile and i.v. anaesthesia during liver resection with inflow occlusion.<sup>47</sup> Although it was a randomized controlled

trial, they had a lower sample size ( $n = 100$ ) than our present study ( $n = 227$ ), and did not adjust their results for steatosis. In our present study we adjusted, amongst other well-known confounders, our results for steatosis and thereby strengthen our conclusion by minimizing the confounding effect. A further interesting point is that Song *et al.* investigated the effect of anaesthetics on I/R injury, but did not look at the effects of different anaesthetics on the clinical outcome such as morbidity or mortality. We investigated the clinical outcome in both groups and showed that neither continuous application of volatile nor i.v. anaesthetics had a beneficial effect on the clinical outcome focusing on any occurred complication, severe complications (grade IIIb–V according to the Clavien-Dindo classification) or 30-days mortality.

In living related donors for liver transplantation, the post-operative outcome was slightly improved after continuous application of the volatile anaesthetic desflurane with a reduction of minor complications such as a pleural effusion, wound haematoma/seroma or hoarseness.<sup>46</sup> Nevertheless, Ko *et al.* also failed to demonstrate any significant differences in serum ALT/AST levels or in severe complications.<sup>46</sup> Yet this study cannot be compared with our present study as inflow occlusion for a minimum of half an hour was not applied in all of the patients, and the patient population was different to our group. Living donors for liver transplantation were healthy persons, whereas our patient population had several additional significant factors influencing the tolerance of I/R injury. For example, more than three-quarters suffered from a malignant disease, and 35.8% received pre-operative chemotherapy.

The mechanism of pharmacological and ischaemic preconditioning in the liver is still unclear and may be explained by numerous possible pathways.<sup>1,48–52</sup> A crucial factor might be the mode and duration of application of volatile anaesthetics, inducing an on-off phenomenon, which could be a prerequisite for hepatic protection. During continuous application of sevoflurane such a trigger might be missing.

One potential hypothesis strongly supported by our recently published RCT,<sup>1</sup> explaining the protective effect of pharmacological preconditioning with volatile anaesthetics is the increased production of nitric oxide (NO), demonstrated by the up-regulation of the inducible (inflammatory) nitric oxide synthase (iNOS).<sup>1,51,52</sup> NO is produced by NO-synthases and plays an important role in the hepatic microcirculation by influencing the liver injury either directly or by blood flow as a vasodilator.<sup>53–55</sup> The literature suggests another potential mechanism in preconditioning involving the enzyme heme oxygenase (HO), which plays a crucial role in the anti-oxidative system in nearly all organs including the liver.<sup>56–58</sup> There are three isoforms of HO enzymes and all three degradation products have a protective function concerning I/R injury.<sup>59</sup> HO-1 can be up-regulated by volatile anaesthetics, especially isoflurane, and thereby the I/R injury of the liver can be reduced after hepatic resection.<sup>60,61</sup> However, we were unable to assess this hypothetical pathway in this retrospective study



because of a lack of liver tissue for further biochemical experiments and examinations. Therefore, not only more experiments in animals are required to clarify the pathway of the protective effect of pharmacological preconditioning on remnant livers but also further RCTs are also required to clarify the superiority or equivalence of ischaemic preconditioning, or intermittent clamping concerning the attenuation of the I/R injury. Also, further RCTs are required to investigate the effect of pharmacological pre-conditioning and the continuous application of volatile anaesthetics and its differences with regard to organ protection and possibly improved outcomes.

Our study is limited by the lack of randomization with the possibility of confounding by indication: (i) to control for confounding we adjusted our results for possible confounders such as age, pre-operative chemotherapy (yes/no), steatosis (yes =  $\geq 5\%$ /no < 5%), ASA score, inflow occlusion time and baseline AST/ALT and bilirubin levels, but we cannot exclude residual confounding. (ii) A variety of confounding variables exist which induce an inhibition (cyclooxygenase-2 inhibitors, non-steroidal anti-inflammatory drugs) or an enhancement (opioids, statins) of cardioprotection.<sup>62</sup> They might also be of a certain importance in liver patients, but were not evaluated. (iii) Another limitation is the limited sample size, which led to rather imprecise estimates. (iv) Furthermore, the higher 30-day mortality in the conditioning group represented a negative selection bias in the sense that continuous volatile anaesthesia was the preferred strategy in patients with a compromised physical status, with multimorbidity, pre-existing liver dysfunction and/or planned major surgery. This is reflected in Tables 2 and 3 and might explain the rather high 30-day mortality rate in the conditioning group. Although this study did not follow a prospectively outlined protocol, we consider the data to be of high quality as the database of the Swiss HPB Center is based on prospectively collected data from consecutive patients and tightly controlled by a database manager.

Using sevoflurane for the entire anaesthesia, this study represents a different modality of sevoflurane application as the preconditioning approach, used in our previous preconditioning RCT, and results from the RCT are therefore not at all comparable with the current data. This observation has also been made in a prospective study in patients undergoing coronary surgery with cardiopulmonary bypass. Sevoflurane preconditioning was compared with sevoflurane post-conditioning and application of sevoflurane for the surgical procedure. An apparent protection was observed in one of the three groups only.<sup>31</sup>

In conclusion, the continuous application of the volatile anaesthetic sevoflurane during liver resection does not offer a protection of the remnant liver from I/R injury compared with the continuous application of the i.v. anaesthetic propofol. These data might also indicate that volatile anaesthetic-induced liver protection is triggered by an on-off mechanism such as pre- or post-conditioning with no effect in a setup of continuous application of volatile anaesthetics.

### Conflicts of interest

The authors declare that there are no conflicts of interest.

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